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14. ABSTRACT

The purpose of this award is to help the principle investigator transition into a long term career in breast cancer imaging research through both training and independent research. The training component of this research has been split into breast imaging and image processing arms. Work within the breast imaging arm has included observation of an NIH funded multi-center breast imaging trial using contrast-enhanced 3D subharmonic imaging for the characterization of mammographically identified breast masses. Clinical training has also included time spent observing breast radiologists perform reads, case and research conferences, and reading breast imaging texts. Within the image processing training component, a Matlab programming training course and separate image processing course were attended and this programming language will be used for the research component of this project.

Subharmonic videos were obtained as part of a larger NIH funded clinical trial. The research

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3 TABLE OF CONTENTS

4 INTRODUCTION

The purpose of this award is to help the principle investigator (PI) transition into a long term career in breast cancer imaging research through both training and independent research. The training portion of this grant consists of both clinical and engineering components. The engineering component focuses on an image processing curriculum under the guidance of the project mentor. The clinical training component includes observation of an NIH funded, multi-center breast imaging trial (data of which will be used in the research portion of this grant), time spent with radiologists specializing in breast imaging, and attendance at clinical research and case conferences. The research portion of this project is to develop computer-based analysis software that will extract physical parameters from a new method of ultrasound imaging (subharmonic imaging) to improve breast lesion characterization. Currently, mammography leads to an unacceptably high rate of false positive findings. Thus, the ultimate goal of this research is to develop subharmonic ultrasound image (SHI) processing algorithms to improve the classification of breast lesions.

5 BODY

5.1 Training Component

The training component of this research has been split into breast imaging and image processing arms. While these arms make up large, distinct portions of the work to date, they are expected to merge as the work shifts to a larger research component in years 2-3.

Work within the breast imaging arm has included the observation of an NIH funded multi-center breast imaging trial using contrast-enhanced 3D subharmonic imaging for the characterization of mammographically identified breast masses. The PI's involvement in the project has included assistance with drafting the protocols, gaining regulatory approval, testing the experimental software, and observing data collection. To date, 49 patients have been observed at Thomas Jefferson University (TJU) and patient enrollment began in late September at the University of California, San Diego (3 subjects enrolled to date). The ability to assist in this process has allowed the PI to gain a better understanding of the requirements for starting and running a large scale breast imaging trial. Additionally the data collected will be used for algorithm development as discussed in the research component.

The PI has also had the opportunity to observe radiologists at TJU's breast imaging center as they interpret mammograms, breast ultrasounds, and breast MRIs. Learning within the clinical environment has also been augmented by working through the texts Kopan's Breast Imaging, and Stravos' Breast Ultrasound under the guidance of the project mentors to better understand current state of breast imaging. This has helped not only to understand the reading process, but also areas for potential future improvements.

Additionally, training within the breast imaging arm of this project has included attendance at TJU's breast case conferences, weekly Kimmel Cancer Center grand rounds, Department of Radiology seminars, and attendance at the 2011 Leading Edge in Diagnostic Ultrasound Breast Ultrasound Tutorial. These presentations have helped the PI gain a larger picture of breast cancer care and emerging areas of research within the field.

Due to the PI's background in engineering the image processing training arm required for this project was less inclusive. Originally, the training curriculum was to include enrollment in the University of Pennsylvania's Graduate Biomedical Image Processing course (UPenn CIS 537- Biomedical Image Analysis). However, due to the timing and release of the award, enrollment in this Fall course was not possible. Instead, the PI and project mentor found it suitable to replace this course with a 3 day Matlab programming training course and a 2 day image processing course both offered by Mathworks (Nattick, MA). These courses not only fit within the required time window, but also dealt exclusively with Matlab (the programming language that will be used for the research component of this project). Additionally, the PI has attended monthly biomedical image processing webinars offered by Matlab to further enhance this skill set. This has greatly helped the PI prepare for the research project focusing on image processing of breast lesions.

5.2 Research Component

While the main focus of year 1 has been on the training component, we have begun preliminary work into the development of algorithms for improving the visualization of blood vessels in 3D subharmonic ultrasound volumes. To date, data has been collected from 52 patients with mammographically identified breast lesions as part of NIH R01 CA140338. Figure 1 shows an example of this data, showing images from a patient's lesion under A) grayscale B-mode, B) color Doppler without contrast, C) Rendered 4D harmonic imaging (HI) prior to contrast injection, D) Rendered 4D HI during contrast wash-in, E) Rendered 4D SHI prior to contrast wash-in, and F)

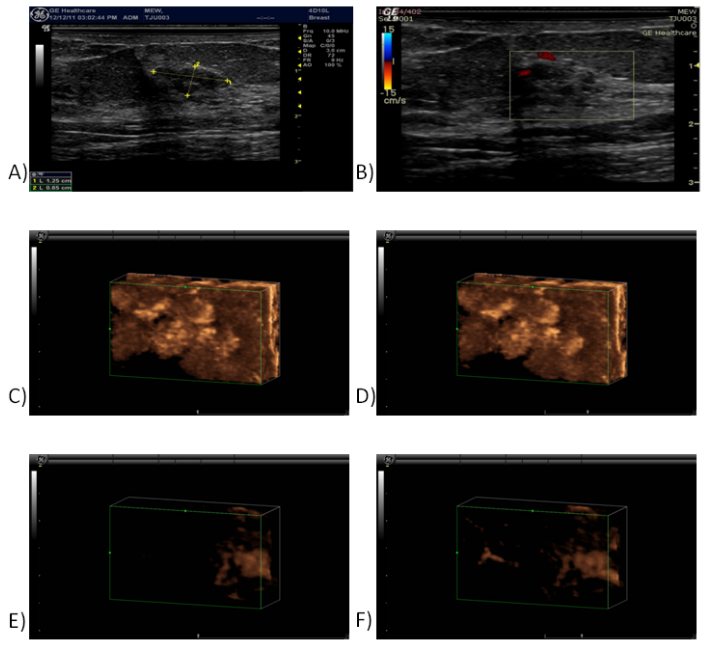

Figure 1. Study showing A) grayscale B-mode with size measurements, B) color Doppler without contrast, C) Rendered 4D HI prior to contrast injection, D) Rendered 4D HI during wash-in, E) Rendered 4D SHI prior to wash-in, and F) Rendered 4D SHI during wash-in.

Rendered 4D SHI during contrast wash-in. As shown by Doppler imaging (Fig. 1B), little flow is located within the actual lesion, although a blood vessel is visualized just to the left. No contrast was detected by HI as shown by the nearly identical images in Fig. 1C and D, presumably due to the high levels of tissue signal apparent throughout the sequence. While little change is observed within the lesion between the pre and post contrast SHI images, the previously identified vessel to the left shows improved enhancement and connectivity within an area of multiple bifurcations. Visualization of these blood vessels would not be possible without the improved levels of tissue suppression afforded in SHI mode.

While these improvements with SHI are evident from the images above, a quantification of SHI's improvement relative to HI was also required. Using data obtained from an *in vitro* flow phantom and renal scanning of canines from a previous optimization study (the data of which was made available to the PI), contrast to tissue ratios (CTR) were calculated. These ratios provide a quantifiable indicator of a physician's ability to differentiate contrast agent from the surrounding tissue and are calculated as:

$$CTR = \frac{2(\gamma_V - \gamma_T)^2}{\sigma_V^2 + \sigma_T^2},$$

where γ_V and γ_T represent the mean backscatter signal strength in the vessel and tissue respectively; and σ^2_V and σ^2_T represent the variance in the respective ROIs [1]. Based on previous optimization work from an in vitro flow phantom and canines, we found SHI resulted in significant improvement in CTR levels relative to HI both *in vitro* (12.11±0.52 vs. 2.67±0.77, $p<0.001$) and *in vivo* (5.74±1.92 vs. 2.40±0.48, $p=0.04$) [2]. This work was not only useful in quantifying SHI's relative improvements, but will also provide a quantifiable metric for future image processing improvements.

Despite the improvements offered by SHI over the current HI industry standard, parametric imaging algorithms are expected to further improve these results. Approval to proceed with the processing of this data took approximately four months and was received by both TJU's Institutional Review Board and the U.S. Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protection Office, who ruled that further processing of these images originally obtained for research purposes did not constitute human research.

Preliminary algorithms have been constructed to process these datasets in order to better visualize the lesion vasculature and blood flow parameters. These parametric maps include maximum intensity projections (MIP), time to peak intensity, perfusion (based on the rate of contrast wash in), and time integrated intensity, which correlates to net blood flow over the contrast wash in cycle. These algorithms have been modified and applied for both 2D compressed representations of the volumes and over the entire volume space. Figure 2 shows an example of MIP processing from data obtained from the case shown in Figure 1. In Fig. 2A, an example of the raw, unprocessed data at midline reveals very little of the total vasculature. Figure2B shows the MIP of this midline slice over the entire

contrast sequence, while c shows the volumetric (3D volume compressed to a 2D place) MIP at contrast wash in. Finally, Fig. 2D shows both the temporal and volumetric MIP. This processing resulted in noticeable enhancement of the vascular structures and is expected to improved SHI's ability to characterize breast lesions.

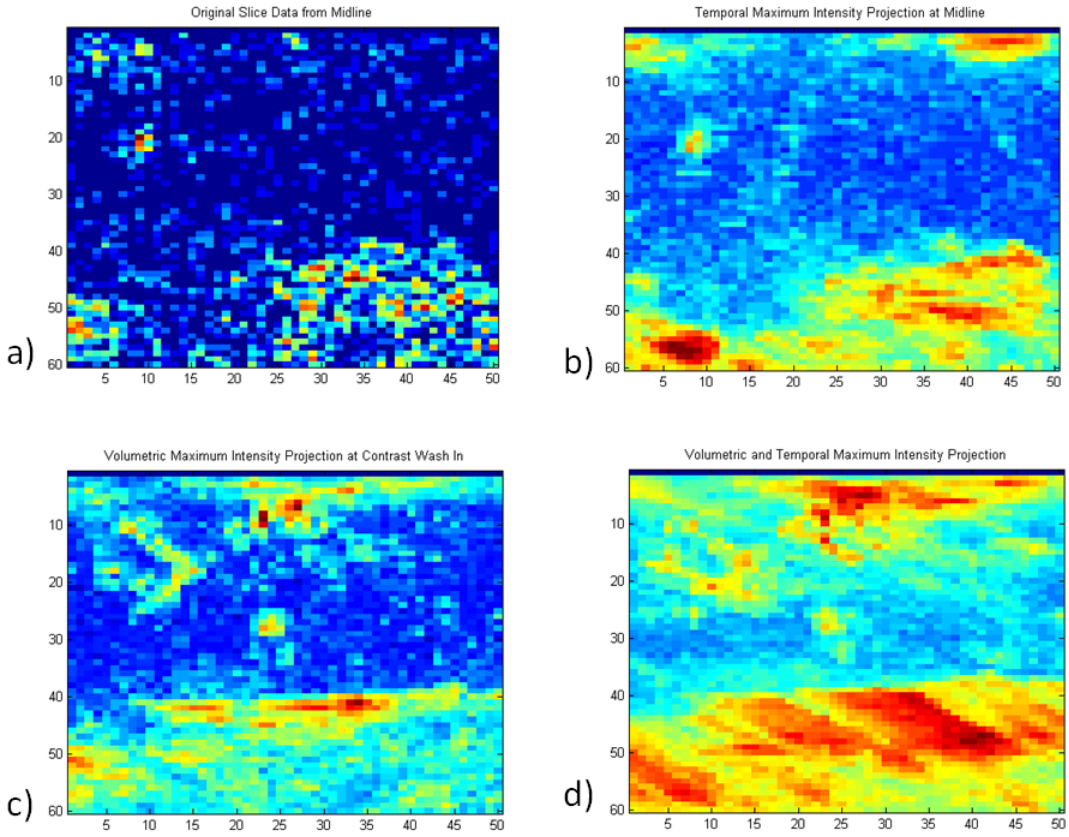

Figure 2. Study showing A) unprocessed slice data at midline from case presented in Figure 1, B) temporal maximum intensity projection at mid line slice, C) Volumetric maximum intensity projection during contrast wash in, and D) Temporal and volumetric maximum intensity projection.

While these results are from first iteration algorithms, they provide improved depiction of lesion vasculature relative to the unprocessed images. Future work will explore motion compensation, filtering approaches, segmentation, and additional quantification such as fractal dimensionality. Additionally, as biopsy results are accumulated for the larger, ongoing RO1 project, the methods will be explored for lesion classification.

6 KEY RESEARCH ACCOMPLISHMENTS

Training Component

- Observation of patient enrollment, site setup, regulatory approval and data collection of a large, multi-center breast imaging trial (data to be used for PI's research project)

- Observation of physician reading of mammograms, breast ultrasounds and breast MRI to better understand diagnostic thought process
- Worked through Kopan's Breast Imaging, and Stravos' Breast Ultrasound to better understand current state of breast imaging
- Attendance at Leading Edge in Diagnostic Ultrasound Breast Ultrasound Tutorial, American Institute of Ultrasound in Medicine 2011 Annual Meeting, as well as the 2011 and 2012 IEEE Ultrasonics Symposium.
- Completion of courses in basic program and image processing using Matlab
- Attendance of Kimmel Cancer Center, Radiology, and Breast Cancer seminars/ case conferences

Research Component

- Quantified contrast to tissue ratios of 4D SHI to directly compare to 4D HI from optimization data
- Developed preliminary algorithms to create maximum intensity projections from 4D SHI datasets which will be used for improving visualization of blood flow
- Developed preliminary algorithms to measure blood flow kinetics based on temporal data.

7 REPORTABLE OUTCOMES

Publications:

1. J.R. Eisenbrey, A. Sridharan, P. Machado, V.G. Halldorsdottir, J.K. Dave, J.B. Liu, S. Park, S. Dianis, K. Wallace, K.E. Thomenius, F. Forsberg. 3D subharmonic imaging in vitro and in vivo. *Acad. Radiol.* 2012; 19:732-739.

2. A. Sridharan, J.R. Eisenbrey, P. Machado, J.B. Liu, V.G. Halldorsdottir, J.K. Dave, H. Zhao, Y. He, S. Park, K. Wallace, K.E. Thomenius, F. Forsberg. Perfusion estimation using contrast enhanced three-dimensional subharmonic ultrasound imaging: an in vivo study. Submitted to Investigative Radiology, October 2012.

Abstracts and Conference Proceedings:

1. J.R. Eisenbrey, J.K. Dave, V.G. Halldorsdottir, A. Sridharan, S. Park, S. Dianis, D.A. Merton, P. Machado, J.B. Liu, J.M. Gonazlez, C. Miller, K.E. Thomenius, D.B. Brown, V. Navarro, F. Forsberg. Simultaneous B-mode/subharmonic imaging and 3D subharmonic imaging on a modified commercial ultrasound scanner. *Proc. IEEE Ultrason. Symp.*, 624-627, 2011.

2. J.R. Eisenbrey, A. Sridharan, D.A. Merton, P. Machado, V.G. Halldorsdottir, J.K. Dave, J.B. Liu, H. Zhao, S. Park, S. Dianis, C.L. Chalek, K.E. Thomenius, F. Forsberg. In vitro and in vivo 4-dimensional subharmonic imaging. *Proc. AIUM Annual Meeting*, J. Ultrasound Med. 31:S50, 2012.

3. C.C. Wilson, J.R. Eisenbrey, R.J. Ro, T.B. Fox, J.B. Liu, S.Y. Chiou, F. Forsberg. Parametric imaging of ultrasound contrast shows an improved correlation with immunohistochemical markers in a glioma model compared to nonparametric imaging. *Proc. AIUM Annual Meeting,* J. Ultrasound Med. 31:S105, 2012.

4. J.R. Eisenbrey, A. Sridharan, P. Machado, D.A. Merton, J.B. Liu, K. Wallace, S. Park, S. Dianis, C.L. Chalek, K.E. Thomenius, F. Forsberg. 4D Subharmonic Imaging In Vivo. *Proc. IEEE Ultrason. Symp.*, 2012.

5. A. Sridharan, J.R. Eisenbrey, P. Machado, J.B. Liu, H. Zhao, Y. He, K. Wallace, S. Park, S. Dianis, C.L. Chalek, K.E. Thomenius, F. Forsberg. Perfusion estimation using 3D subharmonic imaging: an in vivo study. *Proc. IEEE Ultrason. Symp.*, 2012.

Scientific presentations:

1. J.R. Eisenbrey, J.K. Dave, V.G. Halldorsdottir, A. Sridharan, S. Park, S. Dianis, D.A. Merton, P. Machado, J.B. Liu, J.M. Gonazlez, C. Miller, K.E. Thomenius, D.B. Brown, V. Navarro, F. Forsberg. Simultaneous B-mode/subharmonic imaging and 3D subharmonic imaging on a modified commercial ultrasound scanner. IEEE Ultrason. Symp., Orlando, FL, October 2011.

2. C.C. Wilson, J.R. Eisenbrey, R.J. Ro, T.B. Fox, J.B. Liu, S.Y. Chiou, F. Forsberg. Parametric imaging of ultrasound contrast shows an improved correlation with immunohistochemical markers in a glioma model compared to nonparametric imaging. AIUM Annual Meeting, Phoenix Arizona, March 31’st 2012.

3. J.R. Eisenbrey, A. Sridharan, D.A. Merton, P. Machado, V.G. Halldorsdottir, J.K. Dave, J.B. Liu, H. Zhao, S. Park, S. Dianis, C.L. Chalek, K.E. Thomenius, F. Forsberg. In vitro and in vivo 4-dimensional subharmonic imaging. AIUM Annual Meeting, Phoenix Arizona, March 31’st 2012.

Awards and Honors:

1. Thomas Jefferson University Hospital Department of Radiology Judy Dubbs Memorial Research Award. 2012

2. International Contrast Ultrasound Society “Fresh Face Program” Award Winner- International Contrast Enhanced Ultrasound Society Annual Meeting. Chicago September 2012.

3. American Institute of Ultrasound in Medicine Annual Meeting Scientific Poster Session – 2’nd Place (Second Author) March 2012

8 CONCLUSIONS

To date, work generated by this award has mainly focused on the training component with educational components focusing on both breast imaging and image processing. However, basic algorithms and measures of quantification have been applied for improving vascular depictions from 4D breast SHI datasets. As the award progresses, the focus will shift from training to both refinement and application of these image processing algorithms for breast lesion differentiation.

9 REFERENCES

1. Hill CR, Bamber JC, Cosgrove DO. Performance criteria for quantitative ultrasonology and image parameterisation. Clin Phys Physiol Meas 1990; 11:57-72.
2. Eisenbrey JR, Sridharan A, Machado P, et al. 3D subharmonic imaging in vitro and in vivo. Acad. Radiol. 2012; 19:732-739.